Subject: Intensity-Modulated Radiation Therapy (IMRT)

Overview: Intensity-Modulated Radiation Therapy (IMRT) is an extension of three-dimensional conformal radiation therapy (3D-CRT) that changes the intensity of radiation in different parts of a single radiation beam while treatment is delivered. IMRT allows for an increased dose of radiation to the targeted area while reducing exposure to the surrounding normal tissue.

Policy and Coverage Criteria:

Harvard Pilgrim considers Intensity-Modulated Radiation Therapy (IMRT) to be medically necessary for the following conditions:

- Cancers of the anus/anal canal
- Cancers of the abdomen and pelvis when the tumor is in close proximity to organs at risk
- Vulvar malignancies
- Cancer of the prostate
- Cancers of the breast and lung
- Cancers of the head and neck, including thyroid and esophagus
- Cancers of the central nervous system with close proximity to the optic nerve, lens, retina, optic chiasm, cochlea, or brain stem.
- Where critical structures cannot be adequately protected with standard 3-D CRT.

Exclusions: Harvard Pilgrim does not consider IMRT medically necessary for conditions other than those listed above.

Supporting Information:

1. Technology Assessment: ECRI: “Intensity modulated radiation therapy (IMRT) is an external beam radiation treatment that enables clinicians to precisely apply radiation to tumors in doses higher than those used with conventional radiation therapy. IMRT is delivered by a linear accelerator (linac). Under computer control, the individual collimator leaves of the linac slide open and closed, adjusting the beam’s intensity across the radiation field. In a process similar to that of stereotactic radiosurgery, intensity modulation of the beam allows treatment of large or irregularly sized lesions, while minimizing radiation dose to surrounding tissue. IMRT is an advanced form of conformal radiation therapy (CRT). Three-dimensional CRT (3-D CRT) systems are intended to permit high-radiation dosing of tumor tissue, limit dosing of normal tissue, and ultimately improve local control of radiation exposure. IMRT involves adjusting the beam intensity to permit even more conformal dose distributions than CRT. In IMRT, the intensity of the radiation exposure in one portion of the field is modified depending on whether tumor or normal tissue is present in the beam pathway. To do this, IMRT divides the beam into multiple beamlets. The intensity of each beamlet is controlled by the multiple-leaf collimator.”

2. Literature Review: Anus/anal canal: Han et al. (2014) conducted a prospective cohort study to evaluate toxicity, QOL, and clinical outcomes in patients treated with IMRT and concurrent chemotherapy for anal and perianal cancer. Fifty-eight patients were enrolled and there was a median follow-up of 34 months. IMRT reduced acute grade 3+ hematologic and gastrointestinal toxicities compared with reports of non-IMRT patients, without compromising locoregional control. While QOL scores were significantly worse at the end of treatment compared to baseline, scores returned to baseline by 3 months after treatment.
Call et al. (2014) reviewed the records of 152 patients who had IMRT for anal cancer to assess toxicity and efficacy. Data on disease control, toxicity, and treatment characteristics were collected. Acute and late severe toxicity was graded. IMRT with chemotherapy resulted in excellent local control and acceptable severe toxicity rates. Mitchell et al. (2014) conducted a similar study where 65 patients were treated with IMRT and concurrent chemotherapy for localized squamous cell carcinoma of the anal canal. Concurrent chemotherapy and IMRT was well tolerated and was associated with low rates of acute and late toxicity and excellent local control, disease-free survival, and overall survival.

Chuong et al. (2013) conducted a retrospective review of 89 patients with squamous cell carcinoma anal cancer who were treated with either 3D-CRT or IMRT. Long-term outcomes did not differ significantly between treatments, however, a marked decrease in adverse effects and the need for a treatment break was achieved with IMRT.

Abdomen and pelvis: Chen et al. (2015) assessed the toxicity and cost-effectiveness of IMRT compared to 3D-CRT in the postoperative treatment of uterine and cervical cancer. Baseline characteristics, outcome, and ≥CTCAE grade 2 toxicities were compared between 46 patients who received 3DCRT and 34 patients who received IMRT post-hysterectomy. Health states were analyzed at 1, 2, and 3 years post treatment. Toxicity rates were reduced significantly with IMRT compared to 3DCRT. Women who received IMRT had lower rates of late GI and genitourinary toxicity and significantly lower rates of late overall toxicity at 3 years. Treatment costs were higher and toxicity coast lower with IMRT. Chen et al. concluded that IMRT is associated with reduced late overall toxicity compared to 3DCRT without compromising clinical outcome and IMRT is not cost-effective during the early chronic toxicity phase, however, becomes more cost-effective over time.

Lv et al. (2014) compared the efficacy of IMRT, 3-D CRT, and conventional radiotherapy for cervical cancer treatment in a small trial of 16 patients. The IMRT demonstrated superior conformal treatment compared to the 3-D CRT and conventional radiotherapy. Lv et al. concluded that IMRT with appropriate margins encompassing the tumor and potential microscopic pelvic disease reduces the dose to surrounding organs at risk without compromising coverage of the target, therefore, IMRT is an appropriate definitive treatment for patients with cervical cancer.

Casey et al. (2014) reviewed the records of 10 pediatric patients with sarcoma who were treated with whole abdominopelvic radiation therapy (WAP-RT) with IMRT. At a median follow-up of 4 years, both relapse-free survival and overall survival were 100%. A grade 4 hematologic toxicity was found in 40% of patients. Acute GI toxicities were typically grade 1 and were managed with anti-diarrheals and anti-emetics. Due to the excellent rate of tumor control, Casey et al. recommend that all providers give WAP-RT with IMRT to patients with pediatric sarcoma.

White et al. (2014) identified 19 patients with IBD who were treated with abdominal or pelvic external beam radiation therapy. IMRT was used to treat 14 patients and 5 were treated with 3D-CRT. Acute grade ≥2 toxicity occurred in 28% of patients treated with IMRT compared with 100% of patients treated with 3D-CRT. Acute grade ≥2 GI toxicity was lower in patients treated with IMRT (14%) compared to 3D-CRT (100%). Patients with IBD can safely undergo abdominal and pelvic radiation therapy according the these data. The use of IMRT was associated with decreased acute toxicity.

Vulvar: Bloemers et al. (2012) investigated whether IMRT reduces the radiation dose to OAR compared to 3D-CRT in patients with vulvar cancer. IMRT significantly reduced the D(mean), V30, and V40 for all OAR in the adjvant setting. The V45 was also significantly reduced for all OAR except the bladder. For patients treated in the def-group, all IMRT techniques significantly reduced the D(mean), V40, and V45 for all OAR. SIB-IMRT-esc reduced the doses to the OAR compared with seq-3D-CRT but increased the D(max.) for the small bowel, rectum, and bladder. IMRT reduces the dose to the OAR compared with 3D-CRT in patients with vulvar cancer receiving irradiation to a volume covering the vulvar region and nodal areas without compromising the dosimetric coverage of the target volume. IMRT for vulvar cancer is feasible and an attractive option for dose escalation studies. Beriwal et al. (2008) assessed the clinical outcome in 18 patients with stage II-IV A locally-advanced vulvar cancers treated using preoperative chemotherapy with IMRT. Preoperative chemotherapy and IMRT were well tolerated with good clinical response and early clinical outcome. No patients had radiation-related acute or late toxicity of grade ≥ 3.

Prostate: Ratnayake et al. (2014) treated 103 patients with prostate cancer with 3D-CRT (52) or IMRT (51) with doses of 74-78 Gy at 2 Gy per fraction. All patients were treated with IGRT using intra-prostatic gold fiducials.
The patients treated with IMRT had a relative risk of late grade ≥2 rectal toxicity that was 68% less than seen with 3D-CRT at 36 months post treatment. IMRT lead to significantly reduced rectal toxicity compared with 3D-CRT.

Chennupati et al. (2014) assessed late toxicity and QOL for 372 patients receiving definitive IMRT and IGRT for prostate adenocarcinoma. Median follow-up was 47 months. Freedom from Grade 2 GI toxicity was 92% and Grade 2 GU toxicity was 76% at 4 years. Bowel QOL remained stable over the 2-year follow-up period. IMRT with IGRT is associated with low rates of severe toxicity and a high GI and GU QOL. The use of strict rectal constraints can further improve GI QOL and reduce GI toxicity.

Hunter et al. (2013) retrospectively examined late GI and GU toxicity profiles of 333 patients treated definitively and 104 patients treated postoperatively with IMRT and varying IGRT techniques. The median follow-up time was 41 months for definitive patients and 33 months for post-prostatectomy patients. No late grade 4 or 5 GI or GU toxicities were observed. IMRT with IGRT achieved low rates of GI and GU toxicity in both groups of patients. Sheets et al. (2012) examined the comparative morbidity and disease control of IMRT, proton therapy, and conformal RT for primary prostate cancer treatment. Main outcome measures were rates of GI and urinary morbidity, erectile dysfunction, hip fractures, and additional cancer therapy. Men who received IMRT versus conformal RT were less likely to receive a diagnosis of GI morbidities and hip fractures but more likely to receive a diagnosis of erectile dysfunction. IMRT patients were less likely to receive additional cancer therapy. IMRT patients had a lower rate of GI morbidity. There were no significant differences in rates of other morbidities or additional therapies between IMRT and proton therapy. The authors concluded that among patients with non-metastatic prostate cancer, the use of IMRT compared with conformal RT was associated with less GI morbidity and fewer hip fractures but more erectile dysfunction; IMRT compared with proton therapy was associated with less GI morbidity.

Breast and Lung: Lin and Wang (2015) investigated the dosimetric benefits between IMRT and CR among 20 patients with early stage breast cancer receiving breast-conserving surgery. The results of the study demonstrated that whole breast IMRT improves planning target volume dose distribution and improves normal tissue sparing in organs at risk.

He et al. (2014) evaluated the feasibility, early toxicity, initial efficacy, and cosmetic outcomes of 32 patients with early-stage breast cancer who received APBI-IMRT. The median follow-up time was 53 months and no local recurrence or distant metastasis was detected. The most common acute toxicities observed within 3 months after radiotherapy were erythema, breast edema, pigmentation, and pain in the irradiated location, among which 43.8%, 12.5%, 31.3%, and 28.1% were grade 1 toxicities. The most common late toxicities occurring after 3 months until the end of the follow-up period were breast edema, pigmentation, pain in the irradiated location, and subcutaneous fibrosis, among which 6.2%, 28.1%, 21.9%, and 37.5% were grade 1 toxicities. With the exception of one patient, all others had fine or excellent cosmetic outcomes. The results show that APBI-IMRT is a feasible therapy following breast-conserving surgery and the radiotherapeutic toxicity and cosmetic outcomes are acceptable.

Caudrelle et al. (2014) prospectively evaluated the acute and moderately-late cardiac and lung toxicities in 30 patients with stage III breast cancer who received a 5-week course of IMRT-HT. All patients also received adjuvant chemotherapy. The results showed modest skin erythema that was mainly grade 1-2 between the 3rd and 5th week of treatment with 4 patients experiencing grade 3 skin reactions. Only 2 patients demonstrated new grade 1 or 2 dyspnea. The 6-month follow-up chest CT-scans done for 25 out of 30 patients showed minimal anterior lung fibrosis for 7 patients and were completely normal for the other 18. No locoregional recurrence has been recorded and the 5-year survival is 78%. The results showed that IMRT-HT for locoregional breast radiation is very well tolerated with minimal acute or moderately-late side effects. Cardiac and respiratory tests did not show any strong evidence of treatment related abnormalities.

Mast et al. (2013) compared 3D-CRT to IMRT in 20 patients with left-sided breast cancer to investigate whether IMRT enables an additional decrease of cardiac dose in radiotherapy with and without breath-hold. For heart and LAD-region, a significant dose reduction was found in breath-holding. For both breath-holding and free-breathing, a significant dose reduction was found using IMRT.

The Cambridge Breast IMRT trial (Mukesh et al, 2013) investigated late breast tissue toxicity in 1,145 breast cancer patients. Patients were randomly assigned to standard radiotherapy or simple IMRT. Breast tissue toxicities were assessed at 5 year follow-up. Fewer patients in the IMRT group developed suboptimal overall cosmesis and skin telangiectasia compared with standard radiotherapy.
Lei et al. (2013) conducted a prospective Phase II single-arm study on the use of IMRT to deliver accelerated partial breast irradiation. A total of 136 patients with Stage 0/I breast cancer were treated. At 4 year follow-up, ipsilateral breast tumor recurrence was 0.7%; contralateral breast failure 0%; distant failure 0.9%; overall survival 96.8%; and cancer-specific survival 100%. Patients and physicians rated cosmesis as excellent/good in 88.2% and 90.5%, respectively; patients rated breast pain as none/mild in 97.0%. Other observations included edema (1.4%), telangiectasia (3.6%), five cases of grade 1 radiation recall (3.6%), and two cases of rib fractures (1.4%). Four-year results continue to demonstrate excellent local control, survival, cosmetic results, and toxicity profile.

Chen et al. (2014) compared the clinical benefit of IMRT to 3D-CRT for locally advanced stage III non-small-cell lung cancer (NSCLC). Chen et al. concluded that IMRT is increasingly preferred to 3D-CRT when radiation is used to treat locally advanced NSCLC. There was no difference in overall survival or time spent hospitalized following treatment among patients receiving potentially curative radiation.

Head and Neck and CNS: Suh et al. (2014) compared the treatment outcomes of postoperative 3D-CRT and IMRT for patients with maxillary sinus carcinoma. Nineteen patients were treated with IMRT and 35 patients were treated with 3D-CRT. IMRT produced significantly superior radiation dose distribution to planning target volumes that 3D-CRT. IMRT provided significantly better 3-year locoregional recurrence-free survival and distant metastasis-free survival rates compared to 3D-CRT. Suh et al. concluded that postoperative IMRT for patients with maxillary sinus carcinoma resulted in excellent disease control, and should be considered as a first line treatment option.

Trip et al. (2014) compared the effect of AP-PA, 3D-conformal and IMRT techniques on late nephrotoxicity after postoperative chemoradiotherapy for gastric cancer. Eighty-seven patients who were treated were observed; 31 received AP-PA, 25 received 3D-conformal, and 31 received IMRT. Median follow-up was 4.7 years. The mean dose to the left kidney was significantly lower with IMRT. Left kidney function decreased progressively in the total study population, however, occurred at a lower rate with IMRT. Trip et al. found that nephrotoxicity was less severe with IMRT and should be considered as the preferred technique.

Lorentini et al. (2013) compared 3D-CRT and IMRT in patients with glioblastoma (GBM) according to the number of organs at risk (OARs) overlapping the planning target volume (PTV) and investigated the dosimetric impact of different scenarios on the healthy brain tissue irradiation. IMRT and 3D-CRT achieved comparable results in terms of dose homogeneity and conformity. A statistically significant dose reduction to the healthy brain tissue in favor of IMRT was found. IMRT was superior compared to 3D-CRT when there are multiple overlaps between OAR and PTV. IMRT allows for a better target coverage while maintaining equivalent OARs sparing and reducing healthy brain irradiation.

Modesto et al. (2014) conducted a retrospective analysis to determine the value of IMRT in patients with laryngeal and hypopharyngeal squamous cell carcinoma (LHSCC), on outcome and treatment-related toxicity compared to 3D-CRT. Over a five year period, 175 patients were treated with 3D-CRT (90) or IMRT (85). At a median follow-up of 35 months, severe late toxicities were all statistically lower with IMRT compared with 3D-CRT. IMRT for these cancers minimizes late dysphagia without jeopardizing tumor control and outcome.

**Codes:**

**CPT:**

- 77301 – Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specification
- 77338 – Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan
- 77385 – Intensity modulated radiation treatment delivery (IMRT), includes guidance and\ tracking, when performed; simple
- 77386 – Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex

**HCPCS:**

- G6015 – Intensity modulated treatment delivery, single or multiple fields/arcs,via narrow spatially and temporally modulated beams, binary, dynamic mlc, per treatment session
- G6016 – Compensator-based beam modulation treatment delivery of inverse planned treatment using 3 or more high resolution (milled or cast) compensator, convergent beam modulated fields, per treatment session
References:

14. White, EC, Murphy, JD, Chang, DT, Koong, AC. Low toxicity in inflammatory bowel disease patients treated with abdominal and pelvic radiation therapy. Am J Clin Oncol. 2014; Epub.

Summary of Changes

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Approved by UMCPC: 7/26/17
Reviewed/Revised:4/17; 7/17
Initiated:9/15